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Changing patterns of ocular manifestations in HIV seropositive patients treated with HAART

M. ACCORINTI, M.P. PIRRAGLIA, R. CORRADI, C. CORSI, C. FABIANI, P. PIVETTI-PEZZI

Servizio Speciale di Immunovirologia Oculare, Dipartimento di Scienze Oftalmologiche, Università degli Studi di Roma "La Sapienza", Roma - Italy

PURPOSE. *To report the changing patterns of ocular manifestations in human immunodeficiency virus (HIV) seropositive patients treated with highly active antiretroviral therapy (HAART).*
METHODS. *The clinical charts of HIV seropositive patients, 735 examined from 1997 to 2003 and treated with HAART for at least 2 months (Group 1), and 838 untreated examined from 1988 to 1995 (Group 2), were reviewed to assess the frequency of ocular manifestations.*
RESULTS. *HIV-related retinal microangiopathy and opportunistic retinal infections (cytomegalovirus retinitis and toxoplasmic retinochoroiditis) were significantly higher in Group 2 than 1 ($p<0.0001$), while in patients treated with HAART a statistically significant increase in the frequency of chalazion ($p<0.0001$), diabetic and hypertensive retinopathy ($p<0.0001$), lipid arc of the cornea ($p<0.0001$), cataract and glaucoma ($p<0.0001$), and uveitis ($p=0.026$) was observed.*
CONCLUSIONS. *HAART therapy has induced a dramatic decrease in the incidence of HIV-related microangiopathy and opportunistic retinal infection and the occurrence of new lesions related both to the metabolic alterations induced by HAART and to immune reconstitution, such as uveitis. (Eur J Ophthalmol 2006; 16: 728-32)*

KEY WORDS. *Ocular lesions, HIV, HAART therapy, Retinitis, Metabolic alterations*

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INTRODUCTION

In the past the ocular involvement observed in human immunodeficiency virus (HIV) seropositive patients was predominantly related to a severe reduction of the CD4+ cell count and the patients usually sought ophthalmic consult only during the late phase of HIV disease (1, 2). After the introduction of protease inhibitors in 1996 for the treatment of HIV infection, a marked decrease of mortality and morbidity of HIV-infected patients was obtained (3, 4) and both the clinical course of the disease and the ocular lesions changed significantly (5, 6). These drugs, given in various combination with nucleoside analogue reverse-transcriptase inhibitors (highly active antiretroviral therapy [HAART]), allowed in many cases a rehabilitation of the immune system and the development of immune-mediated inflammatory process within the eye (7-11). Nevertheless, protease inhibitors therapy has been associated with hyperlipidemia and accumulation of fat (lipodystrophy syndrome), with increased plasma concentrations of cholesterol, triglycerides, impaired glucose metabolism, and with pancreatic and thyroid dysfunction (12-15). These metabolic changes may theoretically also allow the occurrence of new ocular lesions.

The aim of this study was to evaluate the occurrence of ocular lesions in HIV-seropositive patients treated with

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HAART and to ascertain whether there is a changing pattern of ocular involvement in this patient population.

PATIENTS AND METHODS

The clinical charts of 735 HIV-positive patients treated with HAART, 417 male (56.73%) and 318 female (43.26%) (Group 1), with an average age of 41.6±14.52 years (range 6 months–78 years) examined at the Servizio Speciale di Immunovirologia Oculare, Dipartimento di Scienze Oftalmologiche, Università di Roma "La Sapienza" from 1997 to 2003, were retrospectively reviewed.

The patients at the time of ophthalmic evaluation had assumed HAART continuously for at least 2 months (range 2–60 months). HAART starting criteria were as follows: the occurrence of any opportunistic infection or HIV seroconversion or a CD4+ cell count <350 cells/mmc and a HIV viral load of 55,000 copies (RTPCR).

The patients received saquinavir, indinavir, ritonavir, nelfinavir, Kaletra, nevirapine, efavirenz, lamivudine, didanosine, and stavudine in combination as indicated by their infectious disease specialists.

All patients underwent a complete ophthalmologic examination, including visual acuity assessment, slit lamp biomicroscopy, applanation tonometry, and fundus indirect ophthalmoscopy after pupillary dilation. Additionally, Schirmer's test and break up time (BUT) for the evaluation of tear film abnormalities were performed in all the patients.

Only the data obtained from the first examination of each patient were included in this study.

The data obtained were compared to those from the observation of 838 HIV seropositive patients (Group 2), 656 male (78.28%) and 182 female (21.71%), mean age 34.5±12.34 years (range 6 months–68 years), examined at the same institution and with the same protocol from 1989 to 1995 but who did not take HAART therapy before ocular examination.

Chi-square test and Fisher exact test were used for statistical analysis and p values lower than 0.05 were considered statistically significant.

TABLE I - OCULAR MANIFESTATIONS OF 735 PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS (HIV) TREATED WITH HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) (Group 1) AND OF 838 UNTREATED PATIENTS WITH HIV (Group 2)

Ocular manifestations	Group 1, patients treated with HAART (n = 735), n (%)	Group 2, untreated patients (n = 838), n (%)	p
Tear film abnormalities	221 (30.06)	242 (28.87)	0.645
Chalazion	184 (25.03)	10 (1.19)	<0.0001
Conjunctivitis	38 (5.17)	56 (6.68)	0.248
Keratitis	14 (1.90)	9 (1.07)	0.246
Lipoid arc	92 (12.51)	13 (1.55)	<0.0001
Scleritis/episcleritis	4 (0.54)	0	0.102
Uveitis	13 (1.76)	4 (0.47)	0.026
Cataract	88 (11.97)	11 (1.3)	<0.0001
Glaucoma	37 (5.03)	4 (0.47)	<0.0001
HIV-related retinal microangiopathy	74 (10.06)	344 (41.05)	<0.0001
Retinal opportunistic infection	13 (1.76)	251 (29.95)	<0.0001
CMV retinitis	11 (1.49)	214 (25.53)	<0.0001
Toxoplasmic retinochoroiditis	0	27 (3.2)	<0.0001
HSV/HZV retinitis	0	5 (0.59)	0.099
PCC choroiditis	0	5 (0.59)	0.099
Luetic retinitis	2 (0.27)	0	0.423
Diabetic retinopathy	73 (9.93)	2 (0.23)	<0.0001
Hypertensive retinopathy	103 (14.01)	8 (0.95)	<0.0001
Central retinal vein occlusion	2 (0.27)	3 (0.35)	0.882
Age-related macular degeneration	3 (0.40)	0	0.203
Kaposi's sarcoma	1 (0.13)	4 (0.47)	0.453

RESULTS

The mean age of the patients at the ophthalmic consultation was higher in Group 1 (41.6±14.52 years versus 34.5±12.34 years), and in Group 1 we also noted a significant decrease in the male to female ratio (from 3.6 to 1.3, χ^2: 83.957, p<0.001). Table I reports the frequency of the ocular lesions observed in Groups 1 and 2.

In comparison with untreated patients, those who have received HAART (Group 1) showed a lower incidence of HIV-related microangiopathy (10.06% versus 41.05%, χ^2: 191.05, p<0.0001) and of opportunistic retinal infections (1.76% versus 29.95%, χ^2: 220.68, p<0.0001), especially cytomegalovirus (CMV) retinitis (1.76% versus 25.5%, χ^2: 182.61, p<0.0001) and toxoplasmic retinochoroiditis (0% versus 3.2%, χ^2: 22.223, p<0.0001).

Among the opportunistic retinal lesions, it is of note that cytomegalovirus retinitis was diagnosed in four patients considered unresponsive to HAART, in two who have stopped HAART therapy, and in another five patients who have been treated with HAART for less than 3 months. Luetic uveitis were found in two patients treated with HAART and in none of the 838 untreated patients, while *Pneumocystis carinii* choroiditis and HSV and VZV retinitis were no longer detectable in patients treated with HAART.

In patients treated with HAART, we observed a higher incidence of chalazion (25.03% versus 1.19%, χ^2: 203.64, p<0.0001), lipoid arc of the cornea (12.5% versus 1.55%, χ^2: 73.832, p<0.0001), uveitis (1.76% versus 0.47%, χ^2: 4.96, p=0.026), cataract (11.97% versus 1.3%, χ^2: 73.652, p<0.0001), glaucoma (5.03% versus 0.47%, χ^2: 30.257, p<0.0001), diabetic retinopathy (9.93% versus 0.23%, χ^2: 78.907 p<0.0001), and hypertensive retinopathy (14.01% versus 0.95%, χ^2: 99.832, p<0.0001). The uveitis found in HAART patients was always diagnosed as immune recovery uveitis, being found only in patients with a previous diagnosis of CMV retinitis, while in Group 2 two cases were considered idiopathic, one Fuchs' heterochromic iridocyclitis, and one HIV-related uveitis.

Tear film alterations, including modification of Schirmer's I-test (<10 mm in 5'), BUT (<8 sec), or both, conjunctivitis, keratitis, scleritis and episcleritis, central and branch retinal vein occlusion, age-related macular degeneration, and Kaposi's sarcoma were found in a similar manner in patients treated and untreated with HAART (Tab. I). A total of 199 patients (90%) with a tear film alteration were symptomatic, showing a corneal epithelial keratopathy.

DISCUSSION

Before HAART availability, HIV-related retinal microangiopathy was observed in nearly 50% of the patients and was the most common ocular lesion in this patient group (2-6).

It has been demonstrated that the presence of HIV-related retinal microangiopathy is related to the immunologic status of HIV patients, being statistically correlated with a decrease in CD4+ cell count, with a positive antigenemia and absence of anti-HIV antibodies and with the administration of antiretroviral therapy (16, 17). Therefore the decreasing incidence of retinal microangiopathy in HAART-treated patients from 41.05% to 10.06% (p<0.0001) detected in our patients and also reported by other authors (18) strongly supports the previous observations.

Opportunistic retinal infections, particularly CMV retinitis, accounting for nearly 30% of the ocular manifestations in the pre-HAART period (2-6), now show a dramatic reduction, being detected in only 1.76% of the patients (p<0.0001). Currently CMV retinitis is diagnosed almost exclusively in patients who do not respond to HAART (36.3% in our series), who suspend the treatment (18.18%), or who have been treated for a period of time before ophthalmic consultation insufficient to allow immune recovery (45.45% of the cases). Less frequently encountered, in the pre-HAART period, opportunistic retinal and choroidal infection, such as toxoplasmic retinochoroiditis, *Pneumocystis carinii* choroiditis, and herpetic retinopathies, have disappeared after HAART availability.

Luetic chorioretinitis, which has been detected only in patients treated with HAART, can be considered more related to patient lifestyle than to HIV infection. Furthermore, an increasing incidence of ocular syphilis is currently reported both in HIV positive and negative patients (19).

The increasing incidence of uveitis detected in HAART-treated patients (p=0.026) is due to the therapy-induced immunologic reconstitution. This situation allows the occurrence of a new entity, immune recovery uveitis, which can be detected only in patients with previously diagnosed and treated CMV retinitis. Its supposed pathogenetic mechanism is the stimulation of an immunologic reaction directed towards CMV antigen induced by HAART therapy (6-11).

The high incidence of chalazion (25.03%), hypertensive retinopathy (14.01%), and diabetic retinopathy (9.93%), all statistically more frequent in HAART-treated patients

($p<0.0001$), may be related to a protease inhibitors-induced alteration in lipid metabolism. Protease inhibitors can cause an increased concentration of cholesterol and triglycerides in the serum, impaired glucose tolerance, and diabetes (12-15, 20). Furthermore, the use of HAART has decreased mortality and the progression to acquired immunodeficiency syndrome (21), confirmed also by the increase in the mean age of our patients from 34 years to 41 years, thus allowing an increase in life expectancy, and the onset of ocular lesions typical of advanced age, such as glaucoma, and of advanced age and metabolic changes, such as cataract. Diabetic and hypertensive retinopathy, highly frequent in HAART-treated patients if compared to those untreated, are the direct consequence of the HAART-induced dysmetabolism and may corroborate the hypothesis that the therapy, directly or indirectly, may lead to accelerated coronary artery disease (22).

A significant incidence of tear abnormalities (30% of the cases), both quantitative and qualitative, has been detected in all the patients, either treated or untreated with HAART, and constituted the main cause for seeking an ophthalmic consult by HIV-seropositive patients. Tear film abnormalities may be due to either a direct infiltration of HIV in the lacrimal gland or to an alteration of the lipidic and mucinic layer of the tear, indirectly related to the therapy.

HAART therapy has deeply changed the spectrum of the ocular manifestations in HIV-positive patients. It has turned the potentially life-threatening HIV infection into a chronic one, prolonging significantly the life expectancy of these patients and allowing the outcome of lesions more related to age and metabolic changes, such as cataract and glaucoma, diabetic and hypertensive retinopathy, than to the infection.

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Reprint requests to:
Massimo Accorinti, MD
Servizio Speciale di Immunovirologia Oculare
Dipartimento di Scienze Oftalmologiche
Università degli Studi di Roma "La Sapienza"
Viale del Policlinico 155
00161 Rome, Italy
massimo.accorinti@tiscalinet.it

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